REMARKS

Claim Amendments

Independent claims 158 and 200 have been amended to recite "wherein said conditions of high stringency comprise hybridizing said isolated polynucleotide in 0.015 M NaCl, 1.5 mM sodium citrate, and 0.1 % (w/v) SDS at 50°C, with washes at 42°C in 0.2 x SSC and 0.1% (w/v) SDS." Support for this amendment can be found, for example, at page 25, lines 7-17 of the specification.

Claims 173, 182, 191, 212-218 and 224-230 have been amended to recite at least 90% complementary. Support for this amendment can be found, for example, at page 24, lines 19-20 of the specification.

Claims 169, 171, 173, 178, 180, 182, 187, 189, 191, 196, 198, 210, 222, 224, 234, 241, and 248 have been amended to address informalities.

The amended claims are supported by the application as originally filed. Therefore, this Amendment adds no new matter.

Rejection of Claims 158-235 Under 35 U.S.C. § 112, First Paragraph

Claims 158-235 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner asserts that the claims contain subject matter that was not described in the specification in such a manner as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims read on isolated polynucleotides having particular structural properties, which also encode a protein having a recited binding or functional activity. The Examiner states that "there is no basis in the originally filed specification and claims for the skilled artisan to envision a sufficient number of specific polynucleotide sequences that meet the structural limitations of the claims and which also meet the functional limitations of the claims." (Office Action, page 5, line 19 to page 6, line 1). The Examiner concludes that "[t]he skilled artisan would reasonably have concluded applicants were not in possession of the broadly recited polynucleotides on this basis alone." (Office Action, page 6, lines 1-2).

Rejection of Claims 158–172 and 200-211 Under 35 U.S.C. § 112, First Paragraph

Claims 158–172 and 200-211 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not disclosed in the specification in such a manner as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner states that Claims 158-172 are directed to an isolated polynucleotide comprising a sequence that anneals under "conditions of high stringency" to one of SEQ ID NOS: 1-3, or the complement thereof, and which also necessarily encodes a protein that binds a compound selected for the group consisting of the amino-terminal 40 KDa fragment of Fez1, tubulin, EF1-γ and an amino-terminal 153-amino acid fragment of EF1-γ (Office Action, page 3, lines 1-5). The Examiner further states that Claims 200-211 are directed to an isolated polynucleotide comprising a sequence that anneals under conditions of "high stringency" to a nucleic acid having the sequence of one of SEQ ID NOS: 1-3, or the complement thereof, and wherein the isolated polynucleotide encodes a protein having an activity selected from the group consisting of inhibiting cellular proliferation and tumor suppression. (Office Action, page 3, line 19 to page 4, line 2). Thus, Claims 158-172 and 200-211 are drawn to a genus of isolated polynucleotides that are characterized by the same structural property (i.e., the claimed polynucleotides comprise a sequence that anneals under conditions of high stringency to one of SEQ ID NOS: 1-3, or the complement thereof) and also are characterized as encoding a protein that has one or more binding or functional activities, as recited in the particular claims.

Applicants' specification states that "[u]nder stringent hybridization conditions, only highly complementary nucleic acids hybridize" (see, e.g., specification, page 25, lines 17-18). Exemplary conditions of high stringency are provided in the specification at page 25, lines 7-18. However, to more distinctly define the claimed invention, Applicants have amended independent claims 158 and 200 to recite a specific set of high stringency conditions, i.e., hybridizing in 0.015 M NaCl, 1.5 mM sodium citrate, and 0.1 % (w/v) SDS at 50°C, and washing at 42°C in 0.2 × SSC, 0.1% (w/v) SDS.

With respect to the rejection of Claims 158-172 and 200-211, Applicants direct the

Examiner's attention to the Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, "Written Description" Requirement, 66 FR 1099 (hereinafter, "Guidelines"). Applicants assert that Claims 158-172 and 200-211 are supported by adequate written description for the reasons discussed herein.

The written description requirement is satisfied when the specification describes the claimed invention in sufficient detail so that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Vas-Cath, Inc. v. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). According to the Guidelines, possession of the invention can be shown by "describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention." Guidelines at 1104 (citation omitted). "The description need only describe in detail that which is new or not conventional." Guidelines at 1106 (citation omitted). "An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Id. (citations omitted). The PTO has published training materials that illustrate application of the Guidelines. (Revised Interim Written Description Guidelines Training Materials, hereinafter, "Training Materials", available on line at http://www.uspto.gov/web/offices/pac/writtendesc.pdf

The Court of Appeals for the Federal Circuit recently adopted the PTO standard, articulated in the Guidelines and illustrated in the Training Materials, for determining compliance with the written description requirement for an invention that is described functionally. Enzo Biochem, Inc. v. Gen-Probe Incorporated, 323 F.3d 956 (Fed.Cir. 2002) ("We are persuaded by the Guidelines on this point and adopt the PTO's applicable standard for determining compliance with the written description requirement.").

The Training Materials include Example 9, which illustrates the application of the Guidelines in determining if a claim drawn to a nucleic acid that is defined as hybridizing to a reference nucleic acid, and encoding a protein which has a specific function, is supported by an

adequate written description.

Claims that Recite Hybridization Conditions

Example 9 on page 35 of the Training Materials relates to written description of claims drawn to nucleic acids that are defined as hybridizing to a reference nucleic acid, and encoding a protein which binds a receptor and stimulates its activity. In particular, in Example 9 of the Training Materials, the specification is said to disclose a single cDNA (SEQ ID NO:1), which encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity. (Training Materials, page 35). The specification is further said to include an example where the complement of SEQ ID NO:1 was used under specified hybridization conditions to isolate additional nucleic acids that have the biological activity of SEQ ID NO:1. (Training Materials, page 35). The hybridizing nucleic acids were not sequenced, but they were expressed and several were shown to encode proteins that bind to the receptor and stimulate adenylate cyclase activity. The Example further states that the hybridizing nucleic acids that encode proteins that bind to the receptor and stimulate adenylate cyclase activity may or may not be the same as SEQ ID NO:1. (Training Materials, page 35). The application is said to contain the following claim:

> An isolated nucleic acid that specifically hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO:1, wherein said nucleic acid encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity.

(Training Materials, pages 35-36).

The claim is drawn to a genus of nucleic acids that are defined by function (encodes a protein that binds to a dopamine receptor and stimulates adenylate cyclase activity) and physical/chemical properties (hybridizes under highly stringent conditions to the complement of the sequence set forth in SEQ ID NO:1).

The analysis present in Example 9 of the Training Materials, focuses on whether the specification satisfies the written description requirement by describing a representative number of species within the genus. "Satisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus

in view of the species disclosed." Guidelines, 66 F.R. at 1106.

According to the analysis, SEQ ID NO:1, the single disclosed species encompassed by the claimed genus, is novel and nonobvious and was actually reduced to practice. (Training Materials, page 36). In addition, the specification and claim are said to reveal that:

1) the person of skill in the art would not expect substantial variation among species encompassed by the claimed genus because the highly stringent conditions recited in the claim yield structurally similar DNAs; and

2) highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill in the art are adequate to allow the person skilled in the art to determine that Applicant was in possession of the claimed invention. (Training Materials, page 36-37).

Based on these findings, the specification in this Example is said to disclose a representative number of species, and the written description requirement of 35 U.S.C. § 112 is satisfied. (Training Materials, page 37).

Claims 158-172 and 200-211of the subject application are similar to the claim in Example 9 of the Training Materials in that they define the encoded naturally-occurring Fez1 protein or variant by function (i.e., binds to a compound selected from the group consisting of an amino-terminal 40 KDa fragment of Fez1, tubulin, EF1-γ, and an amino terminal 153-amino acid fragment of EF1-γ and/or has an activity selected from the group consisting of inhibiting cellular proliferation and tumor suppression) and define the claimed nucleic acids by physical/chemical properties that are rooted in the well-known structural relationship of complementary strands of nucleic acids (i.e., hybridizes to a recited reference sequence (e.g., SEQ ID NO: 1, 2, 3, or the complement of any of the foregoing) under the recited conditions).

Applying the analysis from Example 9 of the Training Materials to the claims of the subject application that recite hybridization conditions (e.g., Claims 158-172 and 200-211) reveals that three species (i.e., a *FEZ1* gene sequence, a cDNA reflecting the full-length *FEZ1* mRNA transcript and a cDNA reflecting the *FEZ1* open reading frame) encompassed by the claims are disclosed by nucleotide sequence (SEQ ID NOS:1, 2 and 3, respectively). In addition,

1) the person of skill in the art would not expect substantial variation among species encompassed by the claimed genus because the high stringency hybridization

conditions recited in the claim yield structurally similar DNAs that encode a naturally-occurring Fez1 protein or variant thereof, which binds to a compound selected from the group consisting of an amino-terminal 40 KDa fragment of Fez1, tubulin, EF1-γ, and an amino terminal 153-amino acid fragment of EF1-γ and/or has an activity selected from the group consisting of inhibiting cellular proliferation and tumor suppression; and

2) the recited hybridization conditions, in combination with the well-known structural relationship of complementary strands of nucleic acids, the well-known coding function of DNA and the level of skill in the art, are adequate to allow the person skilled in the art to determine that Applicants were in possession of the claimed invention.

Therefore, like Example 9 of the Training Materials, the instant specification provides adequate written description for claims reciting hybridization conditions (e.g., Claims 158-172 and 200-211).

Rejection of Claims 173-199 and 212-235 Under 35 U.S.C. § 112, First Paragraph

Claims 173-199 and 212-235 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not disclosed in the specification in such a manner as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

In the Office Action, the Examiner states the following:

(i) Claims 173-181 are directed to an isolated polynucleotide comprising a nucleic acid sequence that is "substantially complementary" to SEQ ID NO: 1 and which also necessarily encodes a protein that binds a compound selected for the group consisting of the amino-terminal 40 KDa fragment of Fez1, tubulin, EF1-γ, and an amino-terminal 153-amino acid fragment of EF1-γ (Office Action, page 3, lines 6-10);

(ii) Claims 182-190 are directed to an isolated polynucleotide comprising a nucleic acid sequence that is "substantially complementary" to SEQ ID NO: 2 and which also necessarily encodes a protein that binds a compound selected for the

group consisting of the amino-terminal 40 KDa fragment of Fez1, tubulin, EF1-γ, and an amino-terminal 153-amino acid fragment of EF1-γ (Office Action, page 3, lines 10-14);

(iii) Claims 191-199 are directed to an isolated polynucleotide comprising a nucleic acid sequence that is "substantially complementary" to SEQ ID NO: 3 and which also necessarily encodes a protein that binds a compound selected for the group consisting of the amino-terminal 40 KDa fragment of Fez1, tubulin, EF1-γ, and an amino-terminal 153-amino acid fragment of EF1-γ (Office Action, page 3, lines 14-18);

(iv) Claims 212-223 are directed to an isolated polynucleotide comprising a sequence that is "substantially complementary" to a nucleic acid having the sequence of one of SEQ ID NOS: 1-3, or the complement thereof, and wherein the isolated polynucleotide encodes a protein that inhibits cellular proliferation (Office Action, page 4, lines 3-5); and

(v) Claims 224-235 are directed to an isolated polynucleotide comprising a sequence that is "substantially complementary" to a nucleic acid having the sequence of one of SEQ ID NOS: 1-3, or the complement thereof, and wherein the isolated polynucleotide encodes a protein is a tumor suppressor (Office Action, page 4, lines 6-8).

Thus, Claims 173-199 and 212-235 are drawn to isolated polynucleotides that are "substantially complementary" to either SEQ ID NO:1, 2 and/or 3 and encode a protein that binds a compound selected for the group consisting of the amino-terminal 40 KDa fragment of Fez1, tubulin, EF1-γ, and an amino-terminal 153-amino acid fragment of EF1-γ.

In the Office Action, the Examiner states that "[t]he instant specification teaches that the term 'substantially complementary' is meant to convey a limitation of at least a minimum of 70% complementarity between two nucleic acid sequences." (Office Action, page 4, lines 9-10). The Examiner further states that "there is no direct linkage in the claims between the sequence having the recited complementarity to one of SEQ ID NOS;[sic] 1-3, or the complement thereof, and the encoded protein having the recited binding or functional activity" (Office Action, page 4, line 21 to page 5, line 1), and concludes that "there is insufficient basis for one of ordinary skill in the art

to envision a sufficient number of polynucleotide sequences that have the recited complementarity and which also necessarily encode a protein having the recited activity." (Office Action, page 5, lines 8-10).

Applicants respectfully disagree with the Examiner's assertion. However, in order to expedite prosecution, Applicants have amended independent claims 173, 182, 191, 212 and 224, and dependent claims 213-218 and 225-230, to recite that the claimed isolated polynucleotide is "at least 90% complementary" to a specified nucleotide sequence (e.g., SEQ ID NO:1, 2 and/or 3). As indicated by the Examiner in the Office Action, according to the instant specification, "the phrase 'anneals under high stringency' is meant to convey a limitation of a minimum of at least 75% complementarity between two nucleic acid sequences". (Office Action, page 4, lines 9-10). By amending the rejected claims to recite "at least 90% complementary", Applicants now claim a narrower genus of polynucleotides that are necessarily more similar in structure and/or coding sequence than the nucleotides of the previously-filed claims. Such similarity between nucleotide sequences increases the likelihood that the proteins encoded by those sequences will share one or more of the claimed binding or functional activities.

The specification of the instant application teaches that a person of skill in the art would recognize that certain changes in a nucleotide sequence could be made without changing the amino acid sequence of the encoded protein (see, e.g., specification, page 34, line 23 to page 35, line 31). Furthermore, as taught in the specification, one of skill in the art would recognize that certain changes in a nucleotide sequence could be made, wherein the changes result in one or more conservative amino acid substitutions in the encoded protein, and that such conservative changes are unlikely to appreciably affect one or more of the biological activities of the corresponding wild-type protein (see, e.g., specification, page 51, line 3 *et seq.*).

Claims that Recite Percent Complementarity

Example 14 of the Guidelines relates to written description of claims drawn to a protein and variants thereof, which have a specified catalytic activity. In particular, in Example 14, the specification is said to disclose a single protein that catalyzes the reaction A → B which has been determined to have the amino acid sequence of SEQ ID NO:3 (Guidelines at page 53). The specification contemplates, but does not exemplify, variants having all or any of the following:

substitutions, insertions and deletions. (Guidelines at page 53). The specification is further said to indicate that procedures for producing such variants are conventional in the art and to disclose an assay for detecting the catalytic activity of the protein. (Guidelines at page 53). The application is said to contain the following claim:

> A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B.

(Guidelines at page 53.)

The claim is drawn to a genus of proteins that are defined by function (catalyze the reaction of A → B) and structural features (SEQ ID NO:3, at least 95% identical to SEQ ID NO:3). The analysis presented in Example 14 states that the claim has two generic embodiments (*i.e.*, (1) a protein which comprises SEQ ID NO:3; and (2) variants of SEQ ID NO:3), and focuses on whether the specification satisfies the written description requirement by describing a representative number of species within the genus. (Guidelines at page 54).

According to the analysis, SEQ ID NO:3 is novel and nonobvious, and was actually reduced to practice. (Guidelines at page 54). In addition, the specification and claim are said to reveal that:

1) the genus of proteins that are variants of SEQ ID NO:3 does not have substantial variation because all variants must have at least 95% identity to SEQ ID NO:3 and must have the specified activity; and
2) the single disclosed species (SEQ ID NO:3) is representative of the claimed genus because all members of the genus have at least 95% identity to SEQ ID NO:3 and because an assay suitable for identifying all variants that have the specified activity is disclosed. (Guidelines at page 54).

Based on these findings, the disclosure of Example 14 of the Application of Guidelines is said to meet the written description requirement of 35 U.S.C. § 112 for the claim. (Guidelines at page 55).

As amended, Claims 173, 182, 191, 212-218 and 224-230 are similar to the claim in Example 14 of the Guidelines in that these claims define the variant of a naturally-occurring polynucleotide sequence by structural features (i.e., at least 90% complementary to a nucleic acid having the sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3 and/or the complement of

any of the foregoing) and further define the variant by function (e.g., encodes a protein having a specified binding activity, an ability to inhibit cellular proliferation and/or an ability to inhibit tumorigenesis).

Therefore, based upon the written description contained within the specification of the instant application, one of ordinary skill in the art would reasonably conclude that Applicants had conceived, and were in possession of, a genus of polynucleotides having at least 90% complementarity to a wild-type *FEZ1* gene or coding sequence (e.g., SEQ ID NO:1, 2, 3), which also encode a protein that has one or more of the binding or functional activities specified in the claims.

As such, Applicants' disagree with the Examiner's conclusion that each of Claims 173, 182, 191, 212-218 and 224-230 comprises impermissible new matter (Office Action, page 6, lines 13-14). Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 236-249 Under 35 U.S.C. § 112, First Paragraph

Claims 236-249 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner states that the claims contain subject matter that was not disclosed in the specification in such a manner as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner states that Claims 236-242 are directed to an isolated polynucleotide comprising a nucleotide sequence that encodes a protein comprising SEQ ID NO: 4, and that Claims 243-249 are directed to an isolated polynucleotide comprising a nucleotide sequence that encodes a protein comprising an amino-terminal 40 KDa fragment of the sequence of SEQ ID NO:4 (Office Action, page 7, lines 1-4). The Examiner further states that "there is no literal support in the originally filed specification or claims for claiming literally any nucleic acid sequence that can encode the 596 residue protein represented by SEQ ID NO: 4 or the amino-terminal 40 KDa fragment thereof." (Office Action, page 7, lines 7-9). Applicants respectfully disagree with the Examiner's conclusion that the specification, as originally filed, does not provide literal support for claiming any nucleic acid sequence that can encode the protein of SEQ

ID NO. 4, or the amino-terminal 40 KDa fragment thereof.

The written description requirement is satisfied when the specification describes the claimed invention in sufficient detail so that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Vas-Cath, Inc. v Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). The is no requirement under 35 U.S.C. § 112, that every nuance of the claimed invention be explicitly described structurally in the specification. In fact, the Guidelines to which the Examiner refers Applicants expressly state that "[i]f a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met." (Guidelines, 66 FR 1099, 1106).

As indicated in the specification (e.g., page 18, lines 13-14), and as acknowledged by the Examiner (Office Action, page 7, lines 4-5), SEQ ID NO: 4 represents the amino acid sequence of the full-length, wild-type human Fez1 protein. With respect to Claims 243-249, which are directed to an isolated polynucleotide that encodes a protein comprising an amino-terminal 40 KDa fragment of the sequence of SEQ ID NO:4, the Examiner states that "it is not clear from the cited passages exactly what amino acid sequence from within SEQ ID NO: 4 is encompassed by the phrase 'the amino-terminal 40 KDa fragment of the sequence of SEQ ID NO:4' ." (Office Action, page 7, lines 20-22). However, the specification states that the 40 KDa fragment corresponds to the "amino-terminal 2/3 portion of Fez1 protein" (see, e.g., specification, page 114, lines 12-14). Therefore, the exact amino acid sequence encompassed by the amino-terminal 2/3 portion of the Fez1 protein can be readily identified by one of ordinary skill in the art, because the full-length amino acid sequence of the Fez1 protein is provided as SEQ ID NO: 4 in the specification.

The specification discloses that an isolated polynucleotide that encodes all or a portion of a Fez1 protein (i.e., SEQ ID NO: 4) can exist in various forms, wherein the sequence encoding the Fez1 protein or protein fragment can be linked to one of many different possible nucleotide sequences. For example, an isolated polynucleotide that encodes a human Fez1 protein can be provided as an expression vector, "wherein the region(s) encoding the Fez1 protein are operably linked with a promoter region" (see, e.g., specification, page 47, lines 22-25). Several examples of different promoter sequences that can be linked to the Fez1 coding sequence are provided in

the specification, page 47, line 25 et seq. In addition, the specification teaches that an isolated polynucleotide that encodes a human Fez1 protein of SEQ ID NO:4 can be provided as "substantially any vector known in the art for delivering a nucleic acid to the interior of a cell." (see, e.g., specification, page 48, lines 23-25). Examples of such vectors are listed in the specification, page 48, line 25-27.

The specification further teaches that isolated polynucleotides of the invention can differ in nucleotide sequence and still encode the same Fez1 protein. For example, as shown in the Human Codon Table at page 35, one or more alternate codons can often encode the same amino acid residue. The specification also teaches that when an "isolated polynucleotide of the invention is to be used [as a template] to express all or a portion of a human Fez1 protein . . . it is important that . . . the differences between the sequence of the isolated polynucleotide and the corresponding region of *FEZ1* not result in differences in the encoded amino acid sequence" (see, e.g., specification, page 34, lines 23-29). Thus, Applicants explicitly teach that polynucleotides with different nucleotide sequences can encode the Fez1 protein of SEQ ID NO: 4.

The disclosure in the specification of the instant application clearly teaches that the Applicants' invention encompasses polynucleotides that comprise a Fez1 protein coding sequence that is physically linked to other nucleotide sequences, such as a promoter sequence or a vector sequence. Furthermore, the specification teaches that several polynucleotides that differ in nucleotide sequence can still encode a protein that has the amino acid sequence of SEQ ID NO: 4, or the amino-terminal 40 KDa fragment thereof. Therefore, one of ordinary skill in the art would reasonably conclude that Applicants had contemplated a genus of isolated polynucleotides that encode the protein of SEQ ID NO: 4 or the amino-terminal 40 KDa fragment thereof, as multiple species have been described in the specification. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Supplemental Information Disclosure Statement

A Supplemental Information Disclosure Statement (SIDS) is being filed concurrently herewith. Entry of the SIDS is respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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